



PEDIATRIC DRUG STUDIES:

## Protecting Pint-Sized Patients

Despite seven days, “about 26 hours a day,” spent preparing to testify about the labeling of drugs for children’s use, Wendy Goldberg told Food and Drug Administration experts at a 1997 hearing, “I have become neither a scientist nor a doctor. Not even close.” But, she said, “I do know one thing—I use a lot of medicines on Abby that are not approved by the FDA for use on children her age.”

Of the nine-item laundry list of medicines Goldberg’s 6-year-old daughter Abby was taking for her severe asthma, not a single one was tested or approved in the United States for children under 12. “I feel as though I am testing drugs on my own child, every day, and it isn’t helping anyone,” Goldberg said.

While some drugs do come with pediatric use information (notably, vaccines and antibiotics), asthma medications by no means stand alone in their lack of labeling for kids' treatment. Other types of drugs that often lack pediatric labeling include those for depression, epilepsy, severe pain, gastrointestinal problems, allergic reactions, and high blood pressure.

Overall, more than half of the drugs approved every year that are likely to be used in children are not adequately tested or labeled for treating youngsters, according to FDA estimates. Safety and effectiveness information is especially sparse for the over 7 million children under age 2.

A recent survey by the agency identified the 10 drugs that were prescribed most often to children in 1994 that lacked pediatric labeling. Together, they were prescribed for kids more than 5 million times. (See "Top 10 Drugs Prescribed to Kids Without Pediatric Labeling.")

"At times, children have been harmed and maybe even killed because of a lack of knowledge of how drugs would affect them," says Robert M. Ward, M.D., chair of the American Academy of Pediatrics' Committee on Drugs. Among Ward's historical examples: the deaths of a number of newborn babies in the 1960s when their immature livers were unable to break down the antibiotic chloramphenicol. "Those types of therapeutic misadventures are certainly part of pediatric medicine, and we'd rather they didn't repeat," he says.

To help prevent future chloramphenicol-type disasters, FDA finalized a rule in December 1998 requiring manufacturers of many drugs to provide information about how their drugs can safely and effectively be used in children (from newborns to adolescents), including information on the proper doses for kids.

### A Healthy Dose of Regulation

The pediatric studies rule, published in the Dec. 2, 1998, *Federal Register*, requires that new drugs (generally prescription drugs, including biologics, or drugs derived from living organisms) that are important in the medical treatment of children or will be commonly used in children include labeling information on safe pediatric use.

The information would usually be required when a drug is approved. For drugs already on the market, FDA can require children's studies in certain compelling circumstances—when pediatric labeling could avoid significant risks to kids, for example.

The rule expands on a 1994 regulation that simplified the information needed for a manufacturer to label its drugs for children's use. That rule required drug makers to look at existing data and determine if they could support safe and effective use in children.

"That was the voluntary effort, and we weren't making much headway," says Rosemary Roberts, M.D., chair of the pediatric subcommittee in FDA's Center for Drug Evaluation and Research. "Most manufacturers just went back to saying that safety and effectiveness had not been established for children."

Without pediatric data about a drug, Roberts says, doctors are sometimes reluctant to treat a child with it. "Some physicians won't even try a drug in a child if they don't have enough information," she says. It is legal, however, to prescribe a drug for use in children despite its approval only for adults (termed



"off-label" use).

If doctors decide against using adult drugs in their young patients because the appropriate dose is unknown, children may be deprived of useful treatments, especially some AIDS drugs and other breakthrough therapies that carry considerable risks.

Doctors can be faced with quite a dilemma, says Timothy Westmoreland of the Elizabeth Glaser Pediatric AIDS Foundation. "Do you choose to withhold a potentially effective drug that is useful in adults or expose a child to a drug you don't know is safe?"

Because of their immature organs and different metabolic and immune systems, children react unlike adults to many drugs. Treating children with adult drugs, then, can carry the risk of unforeseen adverse reactions.

Besides the chloramphenicol tragedy, other serious adverse reactions in children have included:

- jaundice in newborns from sulfa drugs
- seizures and cardiac arrest from the local anesthetic bupivacaine
- withdrawal symptoms from pro-

## Top 10 Drugs Prescribed to Kids Without Pediatric Labeling

These 10 drugs were prescribed more than 5 million times in a single year to children in age groups for which the drugs were not adequately labeled.

Drug	Condition	Prescribed
1. Albuterol inhalation solution for nebulization	Asthma	1,626,000 times to children under 12
2. Phenergan	Allergic reactions	663,000 times to children under 2
3. Ampicillin injections	Infection	639,000 times to children under 12
4. Auralgan otic solution	Ear pain	600,000 times to children under 16
5. Lotrisone cream	Topical infections	325,000 times to children under 12
6. Prozac	Depression, obsessive-compulsive disorder	349,000 times to children under 16, including 3,000 times to infants under 1
7. Intal	Asthma	109,000 times to children under 2; aerosol prescribed 399,000 times to children under 5
8. Zoloft	Depression	248,000 times to children under 16
9. Ritalin	Attention deficit disorder, narcolepsy	226,000 times to children under 6
10. Alupent syrup	Asthma	184,000 times to children under 6

(Based on 1994 data from research firm IMS America, Ltd.)

longed use of the painkiller fentanyl

- staining of teeth from the antibiotic tetracycline.

“It can be a real guessing game as to whether we’re treating a child effectively,” Roberts says.

“Sometimes a child’s body will handle the drug very much like an adult’s, she explains, “while other times a child’s body will react quite differently. There may be no way of knowing in advance.”

While dosing information sometimes becomes available to physicians through references such as journal articles and pediatric handbooks, it

may take years for this information to appear. Even then, the information may not be based on adequate testing and may contain gaps, about its use in certain age groups, for example.

Even if the correct dose is known, the medicine will do no good, of course, if a child can’t ingest it. So the 1998 rule in some cases requires manufacturers to make a special formulation of a drug product—liquid or chewable tablet instead of a tablet that must be swallowed whole, for example—to enable kids to take the drug.

Wendy Goldberg knows firsthand the frustrations of treating her child

with drugs made in tablet form for adults. “I need to cut two of them in half,” she told the panelists at the hearing preceding the rule. One, she said, is “like a little stone. I got a gadget from my pharmacist that is supposed to cut it in half, but it doesn’t work exactly right. Do I give her the big “half” or the small “half”? I usually give her the big piece in the morning, on the theory that if something bad happens, at least she’ll be awake.”

### Controlled Risk

To those who point out that bad things can happen during drug studies, too, the American Academy of Pediatrics has responded that treating



**Rx** Safety and effectiveness in pediatric patients have not been established.

**Rx** The effectiveness in pediatric patients with depression or panic disorder has not been systematically evaluated.

**Rx** This product should not be used in children under 2 years because safety for such use has not been established.

**Rx** Tablets are not recommended for use in children under 6 years at this time.

**Rx** Should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

The pediatric study requirement may be waived entirely if a drug is not medically important for children and will not be commonly used in children or if:

- there is strong evidence that the drug product would be ineffective or unsafe in all pediatric patients;
- children's studies are impossible or highly impractical because, for example, the number of patients is too small or geographically spread out;
- attempts to develop a pediatric formulation have failed.

The Pediatric AIDS Foundation's Westmoreland is confident that "virtually all" drugs with significance to children will be studied because of the new FDA rule, as well as the complementary financial incentives under the FDA Modernization Act of 1997, which gives an extra six months of exclusive marketing or patent protection for studying certain drugs in children.

"We see the rule as a real victory," says Janis Stire, executive director of the foundation. "For too long, children have been seen as an afterthought, with so many drugs not available to them. A child is not just half an adult to be given half the adult dose."

children with untested drugs may place more kids at risk than including them in controlled studies of the drugs in the first place.

Children enrolled in drug studies "are sick children that stand to benefit from getting new drugs sooner," says AAP's Ward. "Yes, they will be at risk, just like adults are at risk, if the drug is later found to have problems. But because we're treating children with illnesses, that risk is justified."

Under the rule, the timing of stud-

ies in children will depend on the seriousness of the disease, the availability of other treatments, the amount of safety and effectiveness information already available, and the types of studies that are needed.

FDA will not delay the approval of a drug for adults to await completion of children's studies. Instead, the agency could approve the drug for adults on the condition that the company completes pediatric studies in a timely way.